Notice of Allowability	Application No.	Applicant(s)	
	08/886,044	BHATTACHARJEE ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *Applicants' papers filed 2/18/05*.

2. ☒ The allowed claim(s) is/are *claims 21-28, now renumbered as claims 1-8 respectively*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☒ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☒ to Paper No./Mail Date *paper no. 13-00 1994*.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____.
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☒ Other *Previous IDS 0f 1/23/96*.

ATTACHMENT TO NOTICE OF ALLOWABILITY

Applicants' Response

1) Acknowledgment is made of Applicants' response submitted via the Appeal Brief filed 02/18/05. The arguments therein have been fully considered.

Examiner's Amendment

2) An Examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to Applicants, an amendment may be filed as provided by 37 C.F.R 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee. The authorization to prepare this Examiner's amendment was provided by Mr. Stephen Bent during telephonic interview on 10/14/05. Accordingly, this application has been amended as indicated below:

(a) The first paragraph of the specification as amended via the amendment (C1) filed 06/30/1997 has been replaced with the following:

--This application is a continuation of application 08/230,402, filed 04/20/1994, now abandoned.--

(b) The limitation 'Empigen' at lines 19, 30 and 35 of page 9 and line 4 of page 10 of the specification is replaced with the limitation --EMPIGEN--.

(c) The limitation 'Sephadex' at line 20 of page 8 of the specification is replaced with the limitation --SEPHADEX--.

(d) Claims 1-3, 5-8 and 15-17 have been canceled.

(e) The following new claims 21-28 have been added:

--Claim 21 (New). A vaccine comprising a non-covalent complex of a purified, detoxified lipopolysaccharide endotoxin of *Escherichia coli* strain J5 and a purified outer membrane protein of *Neisseria meningitidis,* wherein said vaccine is effective in immunizing a subject against infection by heterologous Gram negative bacteria by inducing IgG specific to *Escherichia coli* J5 LPS wherein said IgG binds to, or is cross-reactive with heterologous Gram negative bacteria.

Claim 22 (New). The vaccine of claim 21, wherein said *Escherichia coli* strain J5 is of the Rc chemotype.

Claim 23 (New). The vaccine of claim 21, wherein said *Neisseria meningitidis* is group B *Neisseria meningitidis.*

Claim 24 (New). The vaccine of claim 21, wherein the weight ratio of said purified outer membrane protein to said purified detoxified endotoxin in said non-covalent complex is between 1 and 2.

Claim 25 (New). The vaccine of claim 21, 22 or 23 comprising sterile 0.9% sodium chloride or QS21 adjuvant.

Claim 26 (New). A method of actively immunizing a subject against infection by heterologous Gram negative bacteria comprising administering to said subject an immunizing dose of the vaccine of claim 21.

Claim 27 (New). The method of claim 26, wherein said *Escherichia coli* strain J5 is of the Rc chemotype.

Claim 28. (New). The method of claim 26, wherein said *Neisseria meningitidis* is group B *Neisseria meningitidis.*--

Status of Claims

3) Claims 1-3, 5-8 and 15-17 have been canceled via this Examiner's amendment.

New claims 21-28 have been added via this Examiner's amendment.

New claims 21-28 are pending and are under examination.

Rejections Moot

4) The rejection of claims 1-3, 5-8 and 15-17 made in paragraph 8 of the Office Action mailed 09/14/98 and maintained in paragraph 6 of the Office Action mailed 08/19/99 under 35 U.S.C. § 103(a) as being unpatentable over Zollinger *et al.* (US 4,707,543) in view of Ziegler *et al.* (*New Eng. J. Med.* 307: 1225-1230, 1982) or Myers *et al.* (US 4,912,094) and Munford *et al.* (US 4,929,604), is moot in light of cancellation of the claims via this Examiner's amendment.

Response to Applicants' Arguments

5) Applicants' arguments presented via the appeal brief have been carefully considered. Applicants' argument that Zollinger *et al.* disclose a process for preparing a detoxified polysaccharide-outer membrane protein complex from bacterial envelopes, and the so-obtained

products are useful against infection by the *same* bacteria, has been noted. The Office disagrees with Applicants' argument that: (a) all previous attempts to immunize or otherwise protect against LPS endotoxin-mediated pathology had been unsuccessful; and (b) 'Ziegler's results were not due to antibodies against the core region' and 'Ziegler herself was unable to identify antibodies as a basis for the protection observed'. As set forth in paragraph 10 of the Office Action mailed 06/01/00, a thorough review of the prior art shows that Ziegler was indeed able to correlate protection with J5-specific antibody. For instance, Ziegler *et al.* (*In*: *Seminars in Infectious Diseases.* Georg Thieme Verlag, New York, pp. 366-369, 1982, already of record) were able to demonstrate, via adsorption studies, that the protective antibody in the antiserum was directed specifically against the LPS core (see page 368). Ziegler *et al.* also confirmed this "by showing that fully cross-protective antiserum could be prepared by immunization with protein-free purified J5 LPS" (see page 368) (Emphasis added). Ziegler *et al.* also taught the following:

> When compared to non-immune rabbit serum, J5 rabbit antiserum administered intravenously after the onset of *E. coli*, *Klebsiella* or *Pseudomonas* bacteremia strikingly enhanced survival rates even without antibiotics or other supportive measures. In experiments with survival rates less than 10% in animals given nonimmune serum, survival rose to 40 to 70 percent in those treated with J5 antiserum.[13, 14] Antiserum to J5's parent *E. coli* O111, whose core is concealed by side chains, was completely ineffective (see page 368).

Similarly, Marks *et al.* (*J. Clin. Invest.* 69: 742-749, 1982, already of record) also performed adsorption experiments and demonstrated abolishment of passive protection after adsorption of *E. coli* J5 boiled cell antiserum with purified J5 LPS. Marks *et al.* successfully duplicated passive protection using antiserum made by immunization with purified *E. coli* J5 LPS (see first full paragraph on page 743).

Contrary to the above-cited arguments submitted to the Office via their appeal brief, a post-filing publication authored by Bhattacharjee AK, and Cross AS in *Infectious Disease Clinics of North America* 13 (2): 355-369, June 1999 (already of record) states the following with regard to the polyclonal anti-core antibodies (see last full paragraph on page 361):

> Bhattacharjee *et al.* have shown that antibodies produced in rabbits in response to immunization with a killed whole-cell J5 vaccine, when passively infused at onset of fever, protected neutropenic rats against lethal challenge with *P. aeruginosa* 12:4:4 (Fisher immunotype 6).[10] .....These studies suggest that IgG antibody elicited by a vaccine **similar to the one used by Ziegler and colleagues could protect against heterologous sepsis** when given as therapy. [Emphasis added].

These published statements by the inventors too are supportive of the position taken by the Office with regard to the art-known cross-protective nature of the anti-J5 core antibodies produced by

Ziegler's J5 vaccine.

Applicants' discussion of the 2000 Greisman review article has been addressed extensively in the Office Action mailed 06/01/00. Greisman allegedly describes failures of five clinical trials to show broad spectrum protection during Gram negative bacterial sepsis. Applicants argue that Greisman's article effectively rebuts the contention that a skilled artisan would reasonably have expected J5 LPS to act as an effective immunogen in a vaccine preparation to elicit a protective response against a heterologous pathogenic Gram negative bacterium. However, a review of the art at the time of invention and thereafter indicates the following. The above-identified positive results and the results of the adsorption studies obtained both by Ziegler *et al.* (*In*: *Seminars in Infectious Diseases.* Georg Thieme Verlag, New York, pp. 366-369, 1982, already of record) and Marks *et al.* (*J. Clin. Invest.* 69: 742-749, 1982, already of record) are conspicuously absent in the discussions of the Griesman (2000) review article. Furthermore, noteworthy are the comments made by one of the inventors in an *Editorial,* suggesting acknowledgment by at least one of the inventors that positive results were obtained in the past in the original clinical trial(s) with J5 antiserum. For instance, well before the alleged Greisman's evidence against the hypothesis that antibodies to the inner core of lipopolysaccharide in antisera raised by immunization with enterobacterial deep-rough mutants confer broad-spectrum protection during Gram negative bacterial sepsis, and about two years after the publication of Munford's editorial cited by Applicants in their appeal brief, and well after the filing of the parent application 08/230,402, an *Editorial* by Alan S. Cross was published in *Annals of Internal Medicine* 121 (1): 58-60, 1 July 1994. This *Editorial* by Alan S. Cross stated the following (see first full paragraph on page 59):

> In addition to the positive results in the original clinical trial with the J5 antiserum, several retrospective serologic surveys (11, 12) correlated patient survival during gram-negative bacterial sepsis with levels of anti-core glycolipid antibody. In addition, recent experimental studies (13, 14) found protection from lethal sepsis after treatment with antibody directed against core glycolipid epitopes.

The references 11-14 cited above by the Cross *Editorial* are Baumgartner JD. *Infect. Dis. Clin. North Am.* 5: 915-927, 1991; Zinner *et al. J. Infect. Dis.* 133: 37-45, 1976; Pollack *et al. J. Clin. Invest.* 72: 1874-1881, 1983; McCabe *et al. J. Infect. Dis.* 158: 291-300, 1988; Bhattacharjee *et al. J. Infect. Dis.* 1994, respectively. Thus, the Cross *Editorial* expressly acknowledged the role of antibody directed against J5 core glycolipid epitopes in protection from lethal sepsis.

Furthermore, a minireview by A.S. Cross and S. Opal was published in March, 1994 (*J.*

Endotoxin Res. 1: 57-69, March 1994, already of record), i.e., well before the effective filing date of the instant application. Therein, Cross *et al.* taught the following (see paragraph bridging left and right columns on page 64):

> Experimental studies described above achieved highly significant protection in animal models with antibodies directed against both Re[31,80] and J5 LPS.[82] Similarly, serological surveys of bacteremic patients correlated levels of anti-J5[79] and anti-Re[77] antibody at the onset of infection with survival. Thus, there are data to support the efficacy of antibody to both core LPS epitopes.

The references 31, 80, 82, 79 and 77 cited above by the Cross *et al.* minireview are Young *et al. J. Clin. Invest.* 56: 850-861, 1975; McCabe *et al. J. Infect. Dis.* 158: 291-300, 1988; Bhattacharjee *et al. Clin. Res.* 41: 247A, 1993; Pollack *et al. J. Clin. Invest.* 72: 1874-1881, 1983; McCabe *et al. New Eng. J. Med.* 287: 261-267, 1972, respectively. The Cross *et al.* minireview further stated the following (see paragraph bridging left and right columns on page 65):

> Of note, Dale and colleagues reported that following 3 consecutive daily injections of J5 vaccine to a human volunteer, there was a 10-fold increase in IgG anti-J5 antibody that peaked at 9 months, and this IgG was bactericidal for a serum-resistant strain of gonococcus.[95]

It should be noted that the Cross statements made in the above-identified publications are supportive of the position taken by the Office that the cross-protective role of anti-J5 antibody was well known in the art at the time of the invention.

Thus, contrary to Greisman's views and Applicants' assertions of the Greisman's statements, induction of cross-reactive and/or cross-protective antibodies by purified *E. coli* J5 LPS was well demonstrated in the art at the time of the invention as evidenced by the teachings of at least Marks *et al.* (*J. Clin. Invest.* 69: 742-749, 1982). Marks *et al.* provided the *prima facie* evidence that purified J5 LPS does indeed elicit cross-protective antibodies. As set forth at paragraph C) on pages 12 and 13 of the Office Action mailed 06/01/00, the 1982 publication authored by Marks IM, Zielger EJ, Douglas H, Corbeil LB, and Braude AI specifically showed that purified *E. coli* J5 LPS induced antibodies which conferred as potent protection against death due to the heterologous Gram negative bacterium *Haemophilus influenzae* as antiserum to whole *E. coli* J5 cells (see abstract). The teachings by Marks *et al.* that should be particularly noted are the following (see first half of left column on page 743):

> *(b)* Antibody against J5 core LPS protects animals against LPS from *E. coli, Salmonella typhimurium,* and all three major serogroups of *Neisseria meningitidis* (9-11) and against lethal bacteremia due to *E. coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa* (12, 13). *(c)* J5 boiled bacterial vaccine has been administered safely to a large number of adult human subjects without complication, and the human serum obtained after J5

> immunization protects animals and man against death from gram-negative bacteremia (13, 14).
>
> To demonstrate protection by *E. coli* J5-induced immunity we used an experimental mouse infection in which bacteremia, brain infection, and high mortality resemble human HIB disease. Passive protection was abolished after adsorption of J5 boiled cell antiserum with purified J5 LPS, and was duplicated using antiserum made by immunization with purified J5 LPS.

Marks *et al.* further provided the following teachings (see last full sentence in left column on page 747):

> *E. coli* J5 was chosen because it is a readily available and well-characterized source of core glycolipid and has previously been **shown to confer cross-protective effects against diverse gram-negative bacteria and endotoxins** (9-14). [Emphasis added].

The references 9-14 cited in Mark *et al.* are Braude *et al. J. Immunol.* 108: 505-512, 1972; Braude *et al. J. Infect. Dis.* 128: 5157-5164, 1973; Davis *et al. J. Exp. Med.* 147: 1007-1017, 1978; Ziegler *et al. J. Immunol.* 111: 433-438, 1973; Ziegler *et al. Trans. Assoc. Am. Phys. Philadelphia* 88: 101-108, 1975; and Ziegler *et al. Clin. Res.* 29: 576a, 1981.

Marks *et al.* further taught the following (see left column on page 746):

> To be sure that the protective immunogen in J5 boiled cell vaccine is core LPS, we conducted two types of experiments. First, we tested the potency of J5 boiled cell antiserum from which J5 LPS antibody had been removed completely. Then, we evaluated the efficacy of antiserum obtained by immunization with purified J5 LPS.

Marks *et al.* demonstrated 89% and 69% survival in mice passively immunized with antiserum raised against purified J5 LPS (see Table VII). While the antiserum to J5 LPS conferred protection to 14 of 24 mice infected with the heterologous *Haemophilus influenzae* infection, the J5 antiserum adsorbed with J5 LPS failed to confer protection even to one of 24 mice similarly infected (see Table VI). The 31 page-long Greisman review article fails to acknowledge the positive protection results obtained with J5 LPS-induced serum and the adsorption results disclosed both by Marks *et al.* (*J. Clin. Invest.* 69: 742-749, 1982) and Ziegler *et al.* (*In*: *Seminars in Infectious Diseases.* Georg Thieme Verlag, New York, pp. 366-369, 1982, already or record).

The reasons for allowance of the claims, as presented via this Examiner's amendment, are provided below.

Remarks

6) Claims 21-28, now renumbered as claims 1-8 respectively, are allowed.

The following is an Examiner's statement of reasons of allowance. Any comments considered necessary by Applicants must be submitted no later than the payment of the issue fee

and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance".

What is claimed in the instant claims is a combination product comprising a purified, detoxified *E. coli* J5 LPS and a purified *N. meningitidis* outer membrane protein complexed non-covalently. Although Marks *et al.* taught the ready availability of the well-characterized *E. coli* J5 core glycolipid and its ability to confer cross-protective effects against diverse gram-negative bacteria and endotoxins, there was no reasonable motivation for one of ordinary skill in the art at the time of the invention to detoxify Marks' purified native J5 LPS and further non-covalently associate or complex the resultant detoxified J5 LPS specifically with a purified meningococcal outer membrane protein to produce the composition and the active immunization method of the instant invention, particularly given Marks' disclosure that J5 LPS induces antibodies that are also cross-reactive with different serogroups of *Neisseria meningitidis*. Of all the purified microbial proteins, including purified bacterial proteins, available in the art at the time of the invention, no reasonable motivation existed for one of ordinary skill in the art to particularly choose a purified meningococcal outer membrane protein with the art-known purified J5 LPS, after subjecting the native purified J5 LPS to detoxification, particularly in a non-covalent form, to produce the composition and the active immunization method of the instant invention. Therefore, the subject matter of the instant claims, as presented via new claims 21-28, is considered to be non-obvious and patentable. Claims 21-28, now renumbered as claims 1-8 respectively, are allowed.

New claim 21 has descriptive support in the cancelled claim 1, Example 10, and Table 5 of the instant specification. New claims 22-24 have descriptive support in the cancelled claims 2, 3 and 5 respectively. New claim 25 has support in Examples 4 and 8 of the instant specification. New claims 26-28 have descriptive support in the cancelled claims 6-8 and Examples 7 and 8 of the instant specification.

7) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The central Fax number for submission of amendments, responses and papers is (571) 273-8300.

8) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

9) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system. A message may be left on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

October, 2005

S. DEVI, PH.D.
PRIMARY EXAMINER